United States Court of Appeals for the Federal Circuit

INTELLIGENT BIO-SYSTEMS, INC.,
Appellant

v.

ILLUMINA CAMBRIDGE LTD.,
Appellee

2015-1693

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00517.

Decided: May 9, 2016

ROBERT R. BARON, JR., Ballard Spahr LLP, Philadelphia, PA, argued for appellant. Also represented by MARC S. SEGAL; SCOTT DAVID MARTY, Atlanta, GA.

WILLIAM R. ZIMMERMAN, Knobbe, Martens, Olson & Bear, LLP, Washington, DC, argued for appellee. Also represented by JONATHAN EDWARD BACHAND; BRENTON R. BABCOCK, JOSEPH S. CIANFRANI, SHEILA N. SWAROOP, Irvine, CA; NATHANAEL LUMAN, KERRY S. TAYLOR, San Diego, CA.

Before O'MALLEY, WALLACH, and HUGHES, *Circuit Judges.*

O'MALLEY, *Circuit Judge.*

Illumina Cambridge Ltd. ("Illumina") owns U.S. Patent No. 7,566,537 ("the '537 patent"), which is directed to a method of labeling nucleotides in a deoxyribonucleic acid ("DNA") strand. Intelligent Bio-Systems, Inc. ("IBS") filed a revised petition to the Patent Trial and Appeal Board ("Board") requesting *inter partes* review of claims 1–6 and 8 of the '537 patent on August 30, 2013. The Board instituted review of the challenged claims on the basis that they were invalid as obvious under 35 U.S.C. § 103 in view of certain prior art references. In its Final Written Decision, issued February 11, 2015, the Board found that IBS failed to satisfy its burden of demonstrating the obviousness of the challenged claims by a preponderance of the evidence. IBS appeals. Because we find that the Board's judgment was supported by substantial evidence, we affirm.

BACKGROUND

A. Technology

By way of background, DNA is comprised of two strands of nucleotides, which bind to each other to form a double helix structure. "A nucleotide is made up of a sugar molecule, a phosphate, and a 'base.' It is the 'base'—adenine (A), cytosine (C), guanine (G), or thymine (T)—that provides the code for the genetic information in DNA." Appellant Br. 4. The bases of two nucleotide strands pair predictably: A with T, and G with C. In this way, if one knows the identity of a nucleotide in one strand, the identity of the corresponding nucleotide in the other strand is easily inferred. Identification of the sequence of nucleotides in DNA is important, as "the sequence of nucleotides in DNA determines the traits of living organisms." *Id.*

The invention of the '537 patent "relates to labelled nucleotides." '537 patent, col. 1 l. 14. The labels, used to identify the nucleotides, are removable and are intended for "use in polynucleotide sequencing methods." *Id.* at col. 1 ll. 14–16. The polynucleotide sequencing method at issue is the so-called sequencing by synthesis ("SBS") method. SBS "is a process used to identify the sequence of nucleotides in DNA by synthesizing a single strand of DNA using nucleotides that are complementary to the nucleotides in a sample single strand of DNA." Appellee Br. 3.

The claimed method in the '537 patent is directed to labelling nucleotide bases to determine their identity. The 3′-OH ("three prime hydroxyl") position of the sugar components of the labeled nucleotides are further modified with a blocking group (also referred to as a protecting group). The blocking group (or protecting group) attached to the sugar molecule "prevent[s] the natural linking process between nucleotides." Appellant Br. 4. By stopping the linking process, one can detect the label on the nucleotide base and determine its identity (A, C, G, or T). The blocking group is cleavable, which allows the linking process to continue after the label is detected.

The SBS method starts with a single strand of unknown nucleotides and adds complementary nucleotides one-by-one to form the complete, double-helix structure. "The protecting group allows the polymerase to incorporate only one nucleotide at a time into the complementary strand." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, IPR2013-00517, 2015 WL 996355, at *3 (PTAB Feb. 11, 2015) (Final Written Decision of the Board). "By incorporating such modified nucleotides one-by-one into a growing DNA chain, researchers are able to first detect the label to determine the base of each nucleotide, before another nucleotide (with its own label attached to its own base) is added." Appellant Br. 4–5. The identity of the attached label is determined "by any suitable method,

including fluorescence spectroscopy or by other optical means." '537 patent, col. 5 ll. 21–23.

The claims require that "the protecting group comprises an azido group." *Id.* at col. 19 ll. 58–59 (claim 1). According to Illumina, "the inventors of the '537 patent were the first to identify the azidomethyl group (CH_2N_3) as a protecting group that would meet the rigorous requirements of SBS." Appellee Br. 9.

Claim 1, the only independent claim under review, is reproduced below:

> 1. *A method of labeling a nucleic acid molecule*, the method comprising incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule, wherein the nucleotide or nucleoside molecule has a base that is linked to a detectable label via a cleavable linker and the nucleotide or nucleoside molecule has a ribose or deoxyribose sugar moiety, wherein the ribose or deoxyribose sugar moiety comprises a protecting group attached via the 2′ or 3′ oxygen atom, *and said protecting group can be modified or removed to expose a 3′ OH group and the protecting group comprises an azido group*.

Id. at col. 19 ll. 49–59 (emphases added).

B. Prior Art

There are three articles of prior art at issue in this appeal: (1) Roger Tsien et al., WO 91/06678 (May 16, 1991) ("Tsien"); (2) Jingyue Ju et al., U.S. Patent No. 6,664,079 (Dec. 16, 2003) ("Ju"); and (3) Zavgorodny et al., *1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications: A New Versatile Method in Nucleoside Chemistry*, 32 TETRAHEDRON LETTERS 7593 (1991) ("Zavgorodny"). IBS argued to the Board that Ju in combination with Zavgorodny or Tsien in combination with Zavgorodny render the patent invalid as obvious

pursuant to 35 U.S.C. § 103.[1] IBS relied on Tsien and Ju for similar purposes.

In its Decision to Institute, the Board determined that both Ju and Tsien "describe[] a process of labeling, and ultimately sequencing, a nucleic acid molecule" by a polymerase. J.A. 166, 169. Both Ju and Tsien disclose a method of sequencing unknown DNA involving the SBS method, including the labeling of nucleotides for detection and the use of a protecting group at the 3′-OH position of the nucleotide. Neither Ju nor Tsien disclose a protecting group that comprises an azido group, however.

Regarding Zavgorodny, the Board found that it teaches that an "azidomethyl moiety is a suitable protecting group for the 3′ OH position of nucleosides, precisely the position requiring protecting in Ju's [or Tsien's] process, as well as the fact that the azidomethyl group is cleavable from the nucleoside under specific and mild conditions." J.A. 167, 172. As Zavgorodny notes, the "[a]zidomethyl group is of special interest, since it can be removed under very specific and mild conditions, *viz.* with triphenylphosphine in aqueous pyridine at 20 °C." J.A. 861.

Of particular importance to this appeal, Tsien teaches that one of "[t]he criteria for the successful use of 3′-

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[1] The Board also instituted proceedings on the combination of Tsien and Zavgorodny with James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336 (1987), but IBS does not appeal the Board's conclusion that it failed to show "by a preponderance of the evidence that claim 3 of the '537 patent would have been obvious over the combination of Tsien, Zavgorodny, and Prober." *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *13.

blocking groups" is "the availability of mild conditions for rapid and *quantitative* deblocking." J.A. 1010 (emphasis added). In order for the deblocking (i.e., the removal of the protecting group) to be quantitative, it must take place at 100% or near-100% efficiency. Appellant Br. 26 n.10; Appellee Br. 6. Ju similarly notes as a "fundamental requirement" that "the tag and the [protecting] group capping the 3′-OH need to be removed with *high yield* to allow the incorporation and detection of the next nucleotide." J.A. 742, col. 21 ll. 3–16 (emphasis added).

C. The Board's Decision

In its Final Written Decision, the Board construed claim 1 to "encompass[] the use of any protecting group attached via the 2′ or 3′ oxygen atom of a [sugar] moiety, in which the protecting group can be modified or removed to expose a 3′ OH group." *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *4. It also noted that its construction of "claim 1 does not require removal of the protecting group to allow subsequent nucleotide incorporation." *Id.* The parties did not dispute that construction below and do not dispute it here.

The Board then considered whether the combination of Tsien and Zavgorodny rendered claims 1–6 and 8 of the '537 patent invalid as obvious. Based on the teachings of Tsien and Zavgorodny, IBS argued "that an ordinary artisan, 'to improve the efficiency, reliability, and robustness of the sequencing by synthesis method taught in Tsien, would have been motivated to use other protecting groups that meet the criteria of Tsien, such as the azidomethyl group taught by Zavgorodny.'" *Id.* (citation omitted). In addition to contending that an ordinary artisan would be motivated to combine these references, IBS separately asserted that an ordinary artisan would have a reasonable expectation of success in meeting the limitations of the claimed invention by combining Tsien and Zavgorodny. *See id.* at *5 ("[B]ecause an ordinary

artisan would have recognized that Zavgorodny's azidomethyl group met Tsien's criteria for a suitable 3′ OH protecting group, the artisan 'would have expected to succeed in combining the teachings of Tsien and Zavgorodny to carry out'" the claimed invention.) (quoting IBS's Petition, J.A. 146). In its Petition, IBS first addressed whether there was a motivation to combine Tsien or Ju with Zavgorodny and then separately addressed whether an ordinary artisan would have a reasonable expectation of success in meeting the limitations of the claimed invention. J.A. 144–47.

Illumina disagreed with IBS, and argued that an ordinary artisan would not expect the azidomethyl group of Zavgorodny to meet the specific criteria of Tsien or Ju. In particular, Tsien requires "quantitative and rapid removal" of the protecting group, which it understands "to mean essentially 100% removal." *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *5. Prior art of record, however, "demonstrates that an ordinary artisan would have expected Zavgorodny's azidomethyl group to be removed at a much lower efficiency than required by Tsien's methods." *Id.* That prior art reference is known as Loubinoux. *See* J.A. 971–87 (Bernard Loubinoux et al., *Protection of Phenols by the Azidomethylene Group Application to the Synthesis of Unstable Phenols*, 44 TETRAHEDRON 6055 (1988)). Loubinoux reports a 60–80% removal efficiency for azidomethyl groups from phenols using triphenylphosphine. *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *7, *10, *12; J.A. 974–75. 60–80% removal is not quantitative removal within the meaning of Tsien or Ju.

Ultimately, the Board credited Illumina's argument that, given Loubinoux, IBS "has not shown, by a preponderance of the evidence, that an ordinary artisan would have considered it obvious to use Zavgorodny's azidomethyl group as the 3′ hydroxyl protecting group in Tsien's processes." *Id.* at *5. *See also id.* at *12 (finding similarly that IBS failed to establish "that an ordinary artisan

would have considered it obvious to use Zavgorodny's azidomethyl protecting group in the processes described in Ju").

In discussing the legal requirements of obviousness, the Board particularly pointed out the requirement for a reasonable expectation of success:

> [A] conclusion of obviousness requires a reasonable expectation of success:
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> > When there is a design need or market pressure to solve a problem and there are a finite number of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. *If this leads to the anticipated success*, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.
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> [*KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)] (emphases added).
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> As the Court of Appeals for the Federal Circuit has explained, "[a]lthough predictability is a touchstone of obviousness, the 'predictable result' discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose." *Depuy Spine, Inc v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (citations omitted).

Id. at *6. The Board further described Tsien and Zavgorodny, stressing that "the Petition does not point to any specific evidence explaining why an ordinary artisan

would have expected Zavgorodny's azidomethyl protecting group to meet" the quantitative deblocking requirement of Tsien. *Id.* at *7. And as Loubinoux "discloses that removal of an azidomethyl protecting group from a phenolic hydroxyl . . . resulted in deprotected phenols 'as pure products at a yield between 60 and 80%,'" *id.* (citing Loubinoux, J.A. 975), IBS's "Petition did not provide a specific or credible explanation why an ordinary artisan would have expected Zavgorodny's azidomethyl protecting group to meet Tsien's quantitative deblocking requirement under conditions suitable for use in Tsien's sequencing methods," *id.* at *8.[2]

Although the Board's precise legal underpinnings are difficult to discern, it appears to have relied on IBS's failure to demonstrate (1) a motivation to combine the relevant references, (2) that a person of ordinary skill would have a reasonable expectation of success of developing the claimed invention, or (3) both. The Board's opinion conflates these legal issues but its ultimate conclusion is clear. IBS failed to demonstrate that the challenged claims were obvious under the prior art at issue.

In reaching its decision, the Board refused to consider IBS's reply brief and accompanying expert declaration because it found that IBS's reply was improper under two regulations: first under 37 C.F.R. § 42.23(b), which provides that a "reply may only respond to arguments raised in the corresponding opposition or patent owner response," and then under 37 C.F.R. § 42.6(a)(3), which states that "[a]rguments must not be incorporated by

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[2] The Board similarly found that IBS failed to show by a preponderance of the evidence that the claims of the '537 patent were obvious over Ju in combination with Zavgorodny under the same reasoning. *Id.* at *10–12.

reference from one document into another document." *See Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *8–9.

According to the Board, IBS ran afoul of § 42.23(b) by presenting a new argument for the first time in its reply brief. "[T]he Reply presents new issues by changing the unpatentability rationale from express reliance on Zavgorodny's deprotecting conditions, to asserting that those conditions would have been obvious to modify, as well as presenting new evidence to support the new rationale and explain the modifications to Zavgorodny." *Id.* at *9.

The reply, moreover, was accompanied by an expert declaration. According to the Board, the expert declaration "expands on the assertions in the Reply by presenting a number of additional new arguments explaining why quantitative deblocking would have been expected, and cites a number of non-patent literature references which were not relied upon to support unpatentability in the Petition." *Id.* That expert declaration, the Board found, contains "in-depth explanations and supporting documentary evidence" not contained in the reply itself. *Id.* In this way, the Board found, IBS ran afoul of § 42.6(a)(3) by improperly incorporating by reference arguments and evidence from the expert declaration into the reply brief.

IBS now challenges the Board's conclusion that IBS failed to demonstrate the challenged claims were obvious by a preponderance of the evidence. IBS also argues the Board abused its discretion to the extent it found IBS's reply brief improper.

We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

Obviousness is a mixed question of fact and law. Although the Board's ultimate conclusion that the claims are not obvious is a legal determination subject to de novo review, the subsidiary factual findings are reviewed for

substantial evidence. *In re Gartside*, 203 F.3d 1305, 1312, 1316 (Fed. Cir. 2000). "Substantial evidence is more than a mere scintilla." *Consol. Edison Co. v. N.L.R.B.*, 305 U.S. 197, 229 (1938). Substantial evidence review asks "whether a reasonable fact finder could have arrived at the agency's decision" and requires examination of the "record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *In re Gartside*, 203 F.3d at 1312.

"The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) (citations omitted). "The presence or absence of a reasonable expectation of success is also a question of fact." *Id.* Accordingly, the substantial evidence standard of review applies to the Board's resolution of these factual determinations. The Court can review de novo, however, whether the Board "fail[ed] to consider the appropriate scope of the . . . patent's claimed invention in evaluating the reasonable expectation of success." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 966 (Fed. Cir. 2014).

Decisions related to compliance with the Board's procedures are reviewed for an abuse of discretion. *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1121 (Fed. Cir. 2004). "An abuse of discretion is found if the decision: (1) is clearly unreasonable, arbitrary, or fanciful; (2) is based on an erroneous conclusion of law; (3) rests on clearly erroneous fact finding; or (4) involves a record that contains no evidence on which the Board could rationally base its decision." *Id.* Accordingly, the Board's determinations that IBS exceeded the scope of a proper reply in violation of 37 C.F.R. § 42.23(b) and improperly incorporated arguments by reference from another document in violation of 37 C.F.R. § 42.6(a)(3) are reviewed for an abuse of discretion.

A. Motivation to Combine/Reasonable Expectation of Success

The Board found that Zavgorodny would not be "obvious to use" with Tsien or Ju because its azidomethyl group would not be removed quantitatively (at or near 100%). *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *5, *12. IBS argues that, "[b]ecause the claims do not require quantitative cleavage, the Board erred by imposing such a requirement through the reasonable expectation of success analysis." Appellant Br. 38. To the extent the Board's decision is based on the "reasonable expectation of success" requirement, we agree.

The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention. "[F]ailure to consider the appropriate scope of the . . . patent's *claimed invention* in evaluating the reasonable expectation of success . . . constitutes a legal error that [is] review[ed] without deference." *Allergan*, 754 F.3d at 966 (emphasis added). Under the Board's uncontested construction, "claim 1 does not require removal of the protecting group to allow subsequent nucleotide incorporation," let alone quantitative removal. *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *4. Accordingly, it is of no moment that Zavgorodny's protecting group would not be removed quantitatively in Tsien or Ju's sequencing method—removal is simply not required by the claim of the '537 patent. The Board seemed to believe that the "reasonable expectation of success" inquiry looked to whether one would reasonably expect the prior art references to operate as those references intended once combined. That is not the correct inquiry—one must have a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue. The Board's reliance on the absence of a reasonable expectation of success was, thus, improper. *See id.* at *5–6 (citing *KSR*, 550 U.S. at 421 to support the proposition "that a

conclusion of obviousness requires a reasonable expectation of success").

Yet this court "sit[s] to review judgments, not opinions." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540 (Fed. Cir. 1983). And while the Board conflated two different legal concepts—reasonable expectation of success and motivation to combine—it nevertheless made sufficient factual findings to support its judgment that the claims at issue are not invalid. It was IBS's burden to demonstrate both "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.* 688 F.3d 1342, 1360 (Fed. Cir. 2012) (quoting *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotation marks omitted)); *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012). Despite the loose language employed by the Board, its factual findings support its conclusion that the claims are not invalid.

IBS argued in its revised initial petition to the Board that the combination of Tsien or Ju with Zavgorodny was based entirely on a shared purpose: SBS. IBS argued that an ordinary artisan would have a motivation to combine Tsien or Ju with Zavgorodny: "[O]ne of ordinary skill in the art, *in order to improve the efficiency, reliability, and robustness of the sequencing by synthesis method taught in Tsien*, would have been motivated to use other protecting groups that meet the criteria of Tsien, such as the azidomethyl group taught by Zavgorodny." J.A. 145 (emphasis added). This argument follows immediately after IBS lists the "criteria for the successful use of 3′-blocking groups," which includes "quantitative deblocking." J.A. 144.

The Board, therefore, was justified in finding that, "despite having acknowledged the quantitative deblocking requirement in Tsien (Pet. 37), the Petition did not provide a specific or credible explanation why an ordinary artisan would have expected Zavgorodny's azidomethyl protecting group to meet Tsien's quantitative deblocking requirement under conditions suitable for use in Tsien's sequencing methods." *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *8. While this shortcoming is irrelevant to a finding that there was no reasonable expectation of success in meeting the claims of the '537 patent, which do not require quantitative deblocking at all, it is central to a finding of no motivation to combine. This is because the petitioner's *sole* argument for why one of skill in the art would be motivated to combine Zavgorodny's azidomethyl group with Tsien's SBS method was because it would meet Tsien's quantitative deblocking requirement. "When an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references." *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999); s*ee also Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015) ("If all elements of a claim are found in the prior art, as is the case here, the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success.").

There is, moreover, substantial evidence to support a finding that a person of ordinary skill would not have had reason to combine Tsien or Ju with Zavgorodny to achieve the claimed invention. In its decision the Board acknowledged two background references presented by Illumina: Loubinoux, which teaches that azidomethyl methyl groups are removed from phenols with modest efficiency (60-80% yield), and Greene & Wuts, which teaches that

removal of an azidomethyl methyl group from the 3′ hydroxyl position of a deoxyribonucleotide moiety is likely to proceed with even lower efficiency. *Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *7–8 (citing Loubinoux (J.A. 974–75) and Theodora W. Greene & Peter G.M. Wuts, Protective Groups in Organic Synthesis 246–92 (3d ed. 1999) (J.A. 863–970)). These references support a conclusion that the claimed efficiency that allegedly motivated the combination would not be achieved and that a person of ordinary skill in this field would not have been motivated to use the azidomethyl group of Zavgorodny as a "protecting group [that] can be modified or removed to expose a 3′ [hydroxyl] group" of a nucleic acid molecule, as the claim requires. This is so because the azidomethyl group would have been expected to perform inefficiently in that role.

IBS submitted an initial petition that articulated a set of rationales for why the challenged claims were invalid, including why a person of ordinary skill would be motivated to combine the prior art references at issue. IBS made a clear argument as to why a person of ordinary skill would be motivated to combine the prior art references at issue and Illumina demonstrated the error in that argument, which the Board credited. This factual finding by the Board is supported by substantial evidence. The Board did not err in finding that the grounds of invalidity described in IBS's petition were not established.

B. IBS's Improper Reply Brief

IBS also argues that "the Board *must* consider whether it is within the skill of the ordinary artisan to modify the cleavage conditions to satisfy the alleged cleavage requirements." Appellant Br. 44. The Board did not consider this argument, however, because it was raised for the first time in IBS's reply brief and expert declaration.

It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify "with particularity" the "evidence that supports the grounds for the challenge to each claim." 35 U.S.C. § 312(a)(3). "All arguments for the relief requested in a motion must be made in the motion. A reply may only respond to arguments raised in the corresponding opposition or patent owner response." 37 C.F.R. § 42.23(b). Once the Board identifies new issues presented for the first time in reply, neither this court nor the Board must parse the reply brief to determine which, if any, parts of that brief are responsive and which are improper. As the Board noted, "it will not attempt to sort proper from improper portions of the reply." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012).

IBS argued in its petition that "*Zavgorodny* teaches the desired property [in Tsien] that the azidomethyl group 'can be removed under very specific and mild conditions.'" J.A. 145–46 (quoting *Zavgorodny*, J.A. 861). Illumina presented evidence in its response that, "an ordinary artisan would not have considered Zavgorodny's conditions suitably mild for Tsien's sequencing purposes." *Id.* IBS's reply then argued, for the first time, "that an ordinary artisan would have considered it obvious to use deprotecting conditions *other* than those described in Zavgorodny." *Id.* But IBS chose which grounds of invalidity to assert in its petition and it chose not to assert this new one. Unlike district court litigation—where parties have greater freedom to revise and develop their arguments over time and in response to newly discovered material—the expedited nature of IPRs bring with it an obligation for petitioners to make their case in their petition to institute. While the Board's requirements are strict ones, they are requirements of which petitioners are aware when they seek to institute an IPR.

IBS supported its new theory of invalidity by reference to new evidence, citing "a number of non-patent literature references which were not relied upon to support unpatentability in the Petition." *Id.* at *9. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. at 48,767 ("Examples of indications that a new issue has been raised in a reply include new evidence necessary to make out a *prima facie* case for the . . . unpatentability of an original . . . claim, and new evidence that could have been presented in a prior filing."). In these circumstances, we find that the Board did not err in refusing the reply brief as improper under 37 C.F.R. § 42.23(b) because IBS relied on an entirely new rationale to explain why one of skill in the art would have been motivated to combine Tsien or Ju with a modification of Zavgorodny.

Because we conclude that the reply brief and accompanying declaration exceeded the scope of the reply under § 42.23(b), and, therefore, that the Board did not abuse its discretion in excluding those documents, we need not resolve whether the reply brief complied with 37 C.F.R. § 42.6(a)(3), which states that "[a]rguments must not be incorporated by reference from one document into another document." *See Intelligent Bio-Sys., Inc.*, 2015 WL 996355, at *9. Nor do we review the Board's conclusion that, even if proper, the arguments contained in the reply brief are unpersuasive for the same reason it found the arguments in the petition unpersuasive. *Id.* at *10.

CONCLUSION

We find the Board's conclusion that IBS failed to demonstrate by a preponderance of the evidence that the challenged claims of the '537 patent are invalid as obvious over the combination of Tsien and Zavgorodny or Ju and Zavgorodny is supported by substantial evidence. Because the Board correctly determined that IBS failed to carry its burden to establish obviousness of the challenged claims, and because the Board did not abuse its discretion

in finding that IBS's reply brief and accompanying declaration were improper, we need not address IBS's other arguments. Accordingly, we affirm the Board.

AFFIRMED